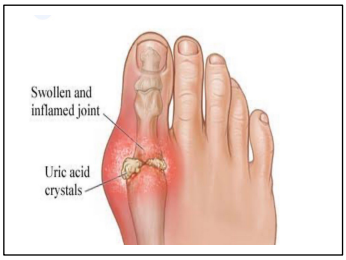
Gout

Sohrab's MRCP pearls:

H/O CKD/ Thiazide/Pyrazinamide + Sudden severe pain, swelling in the 1st MTP joint + Hyperuricemia + Synovial fluid showing MSUM crystals (Needle shaped negative birefringence crystals in plain polarized light) + Synovial fluid WBC- 10,000-50,000/mm3+ Punchedout erosion on X-ray. Diagnosis : Gout

Gout is a form of **microcrystal synovitis** caused by the deposition of **monosodium urate monohydrate (MSUM) crystals** in the synovium. It is caused by **chronic hyperuricemia** (uric acid > 450 µmol/l). Around 70% of first attacks affect in the **first metatarsophalangeal (MTP) joint,** others affected joints are **ankle, wrist & knee.**



⇒ **Predisposing factors:**

1. Decreased excretion of uric acid: (90% of cases of primary gout)
- **Chronic kidney disease**
- Lead toxicity
- Pre-eclampsia
- **Drugs: diuretics (Thiazides), low dose aspirin, pyrazinamide**
- **High alcohol intake** (more than 20 units for men, more than 15 units for women).

2. Increased production of uric acid:
- **Lesch-Nyhan syndrome**
- Myeloproliferative / **lymphoproliferative disorder**
- Cytotoxic drugs
- Severe psoriasis

⇒ **Lesch-Nyhan syndrome**:
- Hypoxanthine-guanine phosphoribosyl transferase (HGPRTase) deficiency
- X-linked recessive disorder
- Features: gout, renal failure, neurological deficits, learning difficulties, self mutilation
- Patients with Lesch-Nyhan syndrome often take allopurinol for lifelong.

3. Drug causes:
- Diuretics: **Furosemide, Thiazides**
- Low dose ASA.
- **Cytotoxic agents: cyclosporine, tacrolimus**
- **Pyrazinamide**

Note:
- **Low dose aspirin may exacerbate gout but high dose aspirin is uricosuric.**
- Aspirin in a dose of 75-150mg is not thought to have a significant effect on plasma urate levels.
- The British Society for Rheumatology recommends it should be continued if required for cardiovascular prophylaxis.

Main causes of gout:

CKD, Thiazide, pyrazinamide ,Alcohol, Aspirin low dose, Lesch-Nyhan syndrome, Cyclosporine, tacrolimus

⇒ Features:

1. Acute gouty arthritis:

- **acute sever pain, erythema, swelling, warmth, High fever**.
- usually occur at **night**, movement restricted.
- commonly affect the joint. **first metatarsophalangeal (MTP) joint.**

2. Chronic gouty arthritis:

- Progressive joints destruction.
- **Tophi formation:** Bone tophi (elbow, knees), **soft tissue tophi (ear pina, tendon sheath)**
- **Uric acid nephrolithiasis** and uric **acid nephropathy** may be developed

⇒ Investigations:

1. Synovial fluid analysis: (gold standard test)

- **Joint fluid aspiration (choice of investigation)** > **Needle shaped negative birefringence crystals** under polarized light Microscopy with **neutrophil.**

2. Uric acid:

- should be checked once acute episode settle down (**typically two weeks later**), as may high, normal, or low during acute attack.
- **Hyperuricemia** may be found.

3. x-ray:

- joint effusion is an early sign.
- well define '**punched out' erosions** with **sclerotic margins (rat bite erosion)**
- relative **preservation of joint space** ,until late disease
- eccentric erosions
- **no osteopenia (in contrast to rheumatoid arthritis)**
- soft tissue **tophi** may be seen.

4. WBC & ESR are typically elevated

⇒ Management:

Rx of Gout in short:

1. In acute attack

1st line: NSAIDs , Colchicine, Steroids

- **Colchicine** (if NSAIDs are contraindicated like patient has CKD, PUD).
- **Steroids** (contraindicated in DM)

2. Urate lowering agents / prophylaxis:

1st line: Allopurinol (give after 1st attack) > if not tolerated or ineffective > **Febuxostat.**
2nd line: Uricosurics (Benzbromarone / Probenecid)
3rd line: Uricase (Pegloticase)

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Management Acute gout flare

1st line drugs: NSAIDs or colchicine or glucocorticoids

1. NSAIDs:

- contraindicated in **CKD** (use **Colchicine** in **mild to moderate CKD** and **prednisolone** in **severe CKD)**
- **gastroprotection** (e.g., a proton pump inhibitor) may also be indicated.

2. Colchicine:

- Mechanism of action: **inhibit microtubule polymerization** by binding to tubulin, interfering with mitosis. Also inhibits neutrophil motility and activity.
- **Useful:** in patient taking **warfarin** or patients have **mild to moderate CKD** but **contraindicated in Severe CKD**
- **Side effect: Diarrhea (main side effect),** myopathy, neuropathy, arrhythmias, cardiac toxicity, myelosuppression.
- **Drug interactions: with statins due p450 3A4 inhibitor >>>** causes **Myotoxicity** >>> so reduced the dose of statins
- **Colchicine** has a **slower onset of action**. The main side-effect is **diarrhoea.**
- The BNF advises to reduce the dose by up to **50%** if creatinine clearance is **less than 50 ml/min** and to **avoid** if creatinine clearance is **less than 10 ml/min.**

3. Glucocorticoids: Prednisolone, methylprednisolone, intraarticular administrations.

- can be used **mild to severe CKD**
- preferable where **intolerance or inadequate response** to **NSAIDs or Colchicine.**
- **avoided in diabetics** because it would **adversely affect the diabetic control**
- intraarticular steroids are preferred for NPO patients.
- a patient with **acute gout and cannot take NSAIDs as he has PUD,** so **Intraarticular steroid injection is the best alternative.**

4. IL-1 blocker:

- **Canakinumab** for patients with contraindication to **NSAIDs or colchicine or glucocorticoids**

5. Rest the affected joints

If the patient is already taking allopurinol, it should be continued & add NSAIDs in acute flare

⇒ Rasburicase:

It is a recombinant **urate oxidase** which may be given during an acute gouty attack without the initial worsening of symptoms. It is also effective newer therapy in **urate nephropathy** in patients undergoing **chemotherapy for haematological malignancy**, it **prevent and treat hyperuricaemia** associated with **tumour lysis syndrome**. Rasburicase **b**reakdown of **uric acid to allantoin** (allantoin is water-soluble and therefore can be renally excreted).

Management of Chronic gouty arthritis

⇒ Urate lowering agents / prophylaxis:

1st line: Allopurinol (give after 1st attack) > if not tolerated or ineffective > **Febuxostat.**
2nd line: Uricosurics (Benzbromarone / Probenecid)
3rd line: uricase (Pegloticase)

⇒ **Indications for urate-lowering therapy (ULT)**

- the British Society of Rheumatology Guidelines now advocate offering urate- lowering therapy to all patients **after their first attack of gout.**

⇒ **ULT is particularly recommended if:**

1. >= 2 attacks in 12 months
2. **tophi present**
3. renal disease
4. uric acid renal stones
5. prophylaxis if on cytotoxics or diuretics

Urate-lowering therapy (ULT)

1st line: Allopurinol & Febuxostat → xanthine oxidase inhibitor

Urate-lowering therapy **should not be started until 2 weeks** after an acute attack, as starting too early may precipitate a further attack. Commencement of ULT is best delayed until inflammation has settled as ULT is better discussed when the '**patient is not in pain'.** Initial dose of 100 mg od, with the dose titrated every few weeks to aim for a serum uric acid of < 300 µmol/l. Lower initial doses should be given if the patient has a reduced eGFR. The BSR guidelines suggest this may need to be continued for 6 months. **when allopurinol is not tolerated or ineffective febuxostat (also a xanthine oxidase inhibitor) is an alternative choice.**

2nd line: Uricosurics: Benzbromarone / Probenecid

- **Uricosurics (Benzbromarone**) Act by blocking the **URAT-1** (Uric acid transporter-1 in Proximal Renal Tubule)

- **Action: Inhibition of uric acid reabsorption** in renal proximal convoluted Tubules → **increased renal elimination of Uric acid**

- Contraindications
  - Nephrolithiasis
  - Moderate to severe CKD

- Side effects: **Urolithiasis (uric acid stones)**

- Interactions: Inhibits penicillin secretion in the proximal convoluted tubule

3rd line: Recombinant Uricase (Pegloticase)

Action: Breakdown of **uric acid to allantoin** (allantoin is water-soluble and therefore can be renally excreted)

Contraindications: G6PD deficiency, Congestive heart failure

Uricase (urate oxidase) is an enzyme that catalyzes the conversion of **urate** to the degradation product of **allantoin** which can **easily pass through urine.** Patients who have **persistent symptomatic and severe gout despite the adequate use of urate-lowering therapy, pegloticase** (polyethylene glycol modified mammalian uricase) **can achieve rapid control of hyperuricemia.** It is given as an infusion once every two weeks.

⇒ **Lifestyle modifications**

- **reduce alcohol intake and avoid during an acute attack**
- lose weight if obese
- **avoid food high in purines** e.g., Liver, kidneys, seafood, oily fish (mackerel, sardines) and yeast products

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Allopurinol

⇒ Side effects of allopurinol:

1) **Allopurinol hypersensitivity syndrome (AHS)**
   - **Non-blanching purpuric rash, hepatic and renal dysfunction, eosinophilia, and vasculitis.** Allopurinol develop **itchy maculopapular rashes,** GIT dysfunction, and deranged liver function tests (LFTs).
2) 20% of patients on allopurinol, who are prescribed **amoxicillin or ampicillin → develop a rash.**

⇒ Allopurinol vs Wafarin vs Colchicine:

- **Allopurinol increases the anticoagulant effect of warfarin**
- If patient was on **warfarin** > **Colchicine** will be the drug of choice.
- Colchicine had little or no interaction with **warfarin**, but a case series was recently published that suggested INR may be increased in some patients prescribed colchicine,
- **patients on warfarin with acute gout > 1st choice: colchicine, 2nd choice: Rasburicase**

⇒ Allopurinol, Azathioprine interaction

Allopurinol **Inhibit xanthine oxidase**. Azathioprine metabolised to active compound of **6-mercaptopurine. Xanthine oxidase** is responsible for the oxidation of 6-mercaptopurine to **6-thiouric acid**. Allopurinol **inhibit xanthine oxidase** can therefore lead to **high** levels of **6-mercaptopurine.** As a result, azathioprine toxicity develop **(Bone marrow suppressed).**

The combination of allopurinol and azathioprine leads to increased bone marrow toxicity

⇒ Gout in patient with DM and CKD:

1. Colchicine

Useful in patients with **renal impairment** who develop gout as **NSAIDs are relatively contraindicated**. The BNF advises to reduce the dose by up to **50%** if creatinine clearance is **less than 50 ml/min** and to **avoid** if creatinine clearance is **less than 10 ml/min.**

2. Prednisolone
- **Adversely affect of diabetic control.**
- Prednisolone can be used instead of NSAIDS if it is contraindicated as in case of **renal impairment or elderly with an increased risk of bleeding with warfarin.**
- Corticosteroids are highly effective, and can be used where **NSAIDs are not tolerated, or in refractory disease (intra-articular, oral, intramuscular, IV).**
- a patient with acute gout and **cannot take NSAIDs as he has PUD**, so **Intraarticular steroid injection is the best alternative**.

⇒ Gout + HTN

If diuretics (thiazides) are being used to treat hypertension an alternative antihypertensive should be considered, consideration should be given to stopping precipitating drugs (such as thiazides) , losartan has a specific uricosuric action and may be particularly suitable for the many patients who have coexistent hypertension

Note:

→ Acute gout pain with **congestive cardiac failure and renal impairment**, developed **severe diarrhoea with colchicine**. The treatment of choice → **Prednisolone**

→ Most patients with hyperuricaemia never develop gout or stones. Treatment of these patients is not recommended.

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Facebook Group: MRCP guidelines with drsohrab

Mentor: Dr. Sohrab